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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,257	04/14/2004	Lindsay H. Burns	14938US02	8108

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
09/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,257	BURNS ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *5, 7, 11-13, 15-21,55-71, 75-76, 78-79, 81-82, 84-86, 88-95, 104-105, 107-110, 128-129, 131-132, 134-140, 142, 152, 154-157, 174-272* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,8,10,14,22-39,41-54,72,74 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,4-8,10-39,41-72,74-79,81,82,84-86,88-95,104,105,107-110,128,129,131,132,134-140,142,152,154-157 and 174-272.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/2008 has been entered.

Currently, claims 1, 4-8, 10-39, 41-72, 74-79, 81-82, 84-86, 88-95, 104-105, 107-110, 128-129, 131-132, 134-140, 142, 152, 154-157, 174-272 are pending and claims 1, 4, 6, 8, 10, 14, 22-39, 41-54, 72, 74 and 77 are under examination.

Response to Arguments

Applicant's arguments over the 35 USC 102 rejection over Levine have been fully considered. Due to Applicant's amendments to the claims, the rejection is withdrawn as the Levine does not teach the combination of an opioid agonist chosen from morphine, oxydone, oxymorphone, hydrocodone or tramadol with an opioid antagonist. Accordingly, the rejection is withdrawn.

Applicant's arguments over the 35 USC 102 rejection over Crain have been fully considered. Applicants have amended claim 1 to include amounts of the opioid agonist and antagonist and assert that Crain does not teach the amounts.

In response to the above arguments, the Examiner notes that Crain does not teach the particular amounts as claimed and the 35 USC 102 rejection is hereby withdrawn. However, Crain does teach that the opioid antagonist potentiates the potency of the opiod agonist; therefore, it would be obvious to optimize the dosage of both compounds to achieve the desired effectiveness (please see the new rejection given below).

Applicant's arguments over the 35 USC 103 rejection over Mitch et al. in view of Romans et al., Sawynok et al., Frome, Fairbanks et al., Rueter et al., and Mayer et al. have been fully considered. Applicants argue that Mitch et al. does not teach compositions comprising an opioid antagonist and an opioid agonist in the amounts as claimed in claim 1. Also, Applicants argue that it is not obvious to use an opioid antagonist in the amounts claimed to enhance the pain alleviating affects of an opioid agonist because an antagonist would be presumed to reduce the pain alleviating effect of the agonist, not enhance it.

In response to the above arguments, it is noted that a new grounds of rejection is given below to address the claims as presently amended. It is noted that it would be obvious that one would ascertain that an opioid antagonist would potentiate the effects of an opioid agonist due to the teachings of Crain et al. As the rejections have been modified, please see the rejection below.

Applicant's arguments over the 35 USC 103 rejection over Goodman & Gilman's has been fully considered. In particular Applicants argue that there is nothing in Goodman & Gilman's that teaches treating neuropathic pain by administering a

composition of claim 1 and that it is not obvious to try to administer an unknown composition via the routes described by Goodman.

The rejection using Goodman & Gilman's was used to teach different routes of administration that are contemplated for all drugs and that it would be well within the skill of the art to contemplate different routes with drugs. Accordingly, the rejection is deemed proper and is maintained below.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 6, 8, 10, 14, 22-39, 41, 42, 44, 45, 47, 48, 49, 50-54, 72, 74, 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crain et al. (US Patent 5,580,876) in view of Mitch et al. (U.S. Patent 5,998,434) and further in view of Romans et al. (7,015,371) and Sawynok et al. (6,211,171) and Frome (2003/0060463) and Fairbanks et al. (6,054,461) and Rueter et al. (2003/0216448) and Mayer et al. (5,502, 058).

Crain et al. teach a method of administering an analgesic or sub-analgesic amount of a bimodally-acting opioid receptor agonist and an amount of an excitatory opioid receptor antagonist formulated in compositions with a pharmaceutically acceptable carrier (meeting the limitation of claims 1, 8; Col. 2, lines 13-20 and Col. 5,

lines 22-25). The agonists and antagonists used in the composition may be in the form of pharmaceutically acceptable acid addition salts (meeting the limitation of claim 4; Col. 5, lines 1-4). Suitable bimodally-acting opioid agonists include morphine (meeting the limitation of claims 1, 10, 14; Col. 4, lines 35-36) and suitable antagonists include naltrexone (meeting the limitation of claims 1, 6, 14; Col. 4, lines 60-62). The composition may include additives (meeting the limitation of claim 36; Col. 5, lines 40-42), diluents (meeting the limitation of claim 37; Col. 5, lines 31-37), and binders (meeting the limitation of claim 38; Col. 5, lines 31-37). The compositions are formulated for oral (meeting the limitation of claim 41; Col. 5, lines 39-47), intravenous, intramuscular and subcutaneous (meeting the limitation of claims 42-45; Col. 5, lines 48-58), and transdermal administration (meeting the limitations of claims 47, 48; Col. 5, lines 59-65). The combination composition is intended for use in humans or animals (meeting the limitations of claims 49-50; Col. 5, lines 8-10). It is obvious that the composition of Crain is administered at least once per day. Crain specifically teaches that the opioid antagonist enhances the analgesic potency of the opioid agonist and attenuates antianalgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects associated with the administration of the agonist (Col. 2, lines 8-20).

Crain et al. does not teach the addition of gabapentin, desipramine, ketamine, anti-dynorphin antibodies, A-85380, bupivicaine hydrochloride, a colloidal dispersion system, a plasticizer, intrathecal or epidural or perineural administration, daily administration, allodynia as the type of neuropathic pain or the dosage amounts of the opioid agonist or antagonist.

Mitch et al. teach a method for treating pain in which it is taught that opioid antagonists and opioid agonist-antagonist combinations are useful (Col. 27, lines 54-57). Preferred opioid antagonists include naltrexone and a preferred agonist is morphine (Col. 27, lines 57-61). Mitch et al. further teach that non-steroidal anti-inflammatory drugs, including aspirin and ibuprofen, are also useful in the compositions of the invention (meeting the limitations of claims 24-26; Col. 27, lines 23-29). It is taught that compositions of the invention are useful in the sciatic nerve ligation model, which is an animal model to treat allodynia (meeting the limitations of claims 54, 77; Col. 32, 15-35). The compositions of the invention include a colloidal dispersion system (meeting the limitation of claim 35), a diluent (meeting the limitation of claim 37), a binder (meeting the limitation of claim 38), a plasticizer (meeting the limitation of claim 39) and preservatives (meeting the limitation of claim 36; Col. 31, lines 40-64). The compositions can be administered orally, intravenously, intramuscularly, subcutaneously and transdermally (meeting the limitation of claims 42, 44-45, and 47-48; Col. 27, lines 14-19). The compound can be administered to mammals and humans (meeting the limitation of claims 49-50; Col. 31, lines 54-57). It is further taught that active compounds will be administered in a dose range of 0.005 to about 500 mg/kg of body weight (Col. 27, lines 2-3).

Romans et al teach a method of treating neurogenic pain, including mechanical allodynia (Col. 7, lines 3-6) using von Frey testing for pain behavior (Col. 7, lines 35-37). Morphine sulfate and gabapentin were tested for analgesia in mechanical allodynia and

analgesia was observed after administration of morphine and gabapentin (meeting the limitation of claims 22-23; Table 1).

Sawynok et al. teach a method of producing analgesia using tricyclic antidepressants, with desipramine being a preferred compound (meeting the limitation of claim 27; Col. 9, lines 23-26, 66-67 and Col. 10, line 1). Desipramine was tested in the spinal nerve ligation model of neuropathic pain (Col. 12, lines 53-59).

Frome et al. teach a method of treating allodynia with ketamine (meeting the limitation of claims 28-29; paragraph 0084, 0086 and 0090).

Fairbanks et al. teach that allodynia can be induced by dynorphin (Col. 3, lines 6-7); therefore it would be obvious that an anti-dynorphin antibody would be produced as an immune response to pain (meeting the limitation of claims 30-31).

Rueter et al. teach a method for pain reduction (including allodynia; paragraph 0030, 0033). The NNR agonist A-85380 was used in a model of neuropathic pain (meeting the limitation of claim 32; Example 3).

Mayer et al. teach the use of the compounds such as ketamine (Col. 3, line 39) and bupivicaine hydrochloride (meeting the limitations of claims 33-34; Col. 6, lines 28-29) to treat neuropathic pain, which is defined as hyperalgesia or allodynia (Col. 1, lines 28-42).

Furthermore, it is obvious to vary and/or optimize the amount of naltrexone and morphine provided in the composition, according to the guidance provided by Crain et al. and Mitch et al., to provide a composition having the desired properties such as the desired concentrations of opioid antagonist and opioid agonist to effectively treat

allodynia. It is also obvious to vary and/or optimize the dose of opioid antagonist that will enhance the potency of the opioid agonist per the teachings of Crain et al. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of the prior art references because each reference individually teaches the various compounds for treating allodynia, a form of neuropathic pain. It is prima facie obvious to combine compositions each of which is taught by the prior art to be useful for the same purpose (treatment of allodynia), in order to form a composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980). Furthermore, one would be motivated to combine opioid antagonists with the various compounds listed in an effort to maximally treat allodynia.

Claims 43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman & Gilman's: The Pharmacological Approach to Therapeutics (Tenth edition, page 8).

Goodman & Gilman's teaches various common routes of drug administration therefore making it obvious to utilize any route for drug administration of the present invention (pages 5-8).

Accordingly it would have been obvious to one having ordinary skill in the art at the time of the invention to administer the claimed composition by any known route of drug adminisration as is taught in Goodman & Gilman's. One would have been motivated to provide drug delivery any known form in order to achieve the most rapid effect of the drug.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

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